



Armed Forces College of Medicine AFCM





Myasthenia Gravis

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INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

1- Classify the drugs used in treatment of myasthenia gravis

2- Explain the mechanism of action and adverse effects of drugs used in treatment of myasthenia gravis



Introduction



- **Myasthenia gravis (MG)** is an autoimmune disorder affecting neuromuscular transmission, Leading to generalized or localized muscle weakness characterized by easy fatigability, Severe disease may affect all the muscles, including those necessary for respiration.
- **It is due to production of auto-antibodies against acetylcholine receptors** (antibodies against Motor End Plate (M.E.P.)). In this disease, antibodies are produced against the main immunogenic region found on $\alpha 1$ subunits of the nicotinic receptor channel complex. **Antibodies are**



Introduction



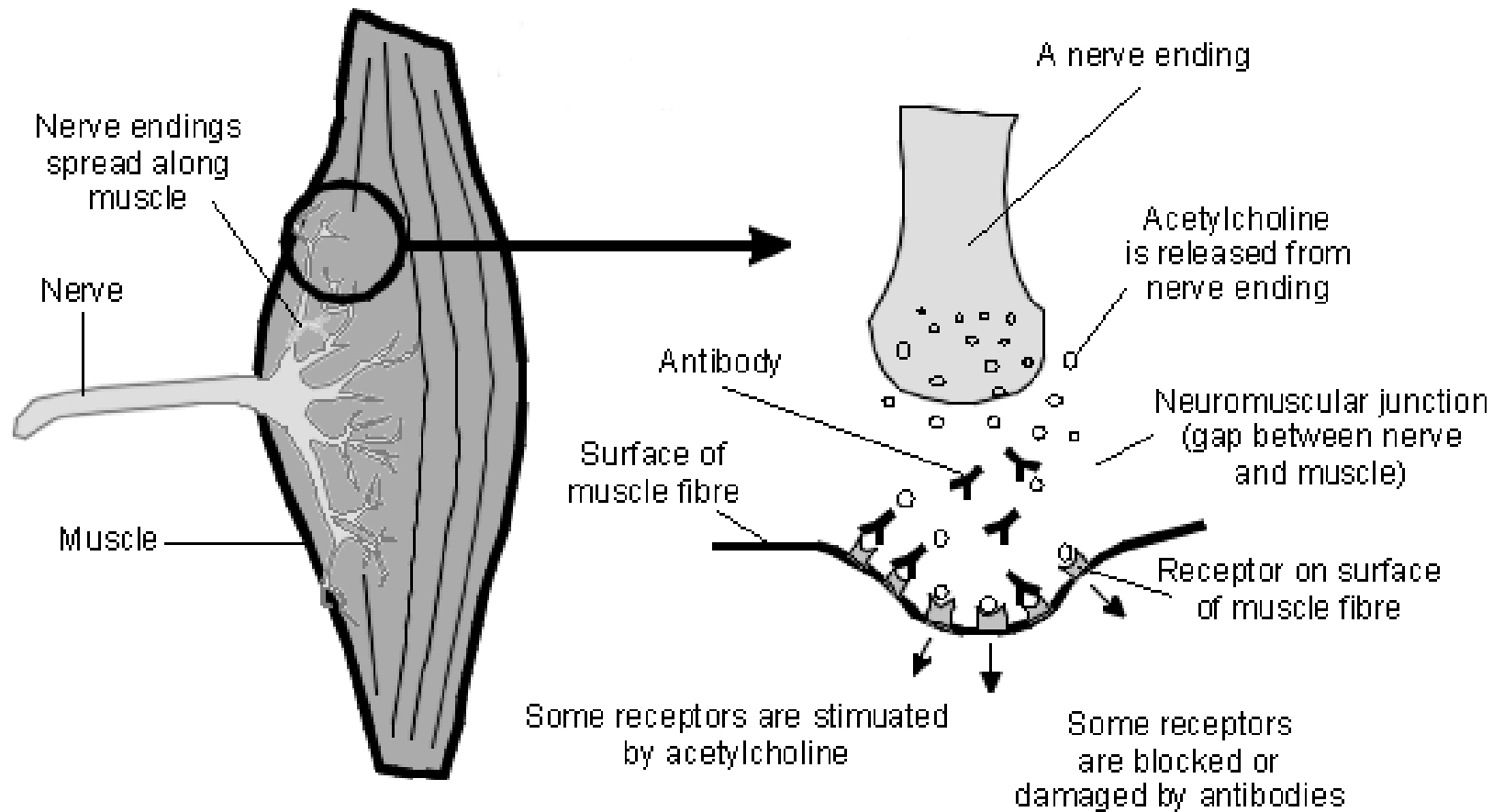
The antibodies reduce nicotinic receptor function by:

- (1) Cross-linking receptors, a process that stimulates their internalization and degradation
- (2) Causing lysis of the postsynaptic membrane
- (3) Binding to the nicotinic receptor and inhibiting function.

Frequent findings are ptosis, diplopia, difficulty in speaking and swallowing, and extremity weakness



Introduction

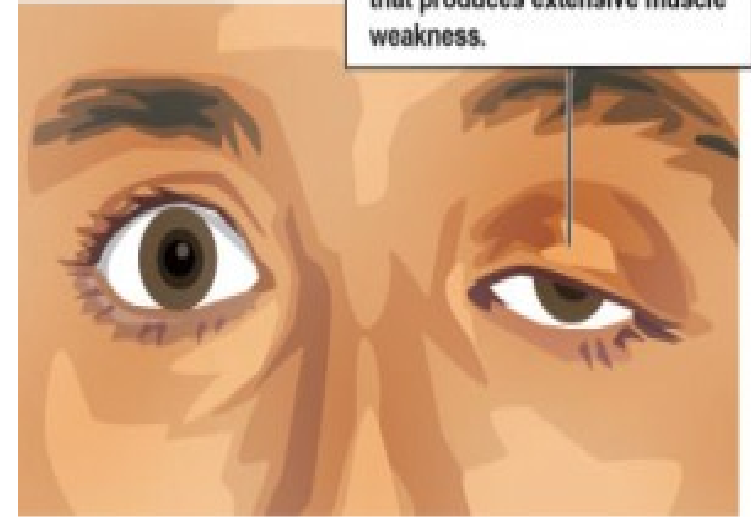


Clinical Picture



- Fatigue with muscle use
- Double vision, droopy eyelids, trouble swallowing/chewing
- Facial weakness
- Shortness of breath
- **Myasthenic crisis** is a complication of myasthenia gravis characterized by worsening of muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation

A drooping eyelid, is the most frequent early sign of myasthenia gravis, a disease that produces extensive muscle weakness.



Cholinergic and Myasthenic crisis



Cholinergic crisis	Myasthenic crisis
Due to: Excessive ChE inhibition (over dose) → Maintained depolarization at N-M junction.	Due to: Insufficient treatment with: Choline esterase inhibitors.
I.V Edrophonium → produces more weakness.	I.V Edrophonium → produces muscle improvement.



To differentiate between cholinergic and myasthenic crisis:

Edrophonium IV is used.

- It is a **Reversible** choline esterase inhibitor.
- Shortly** acting (duration 5 min).

Also, Edrophonium can be used as a pharmacological test in **diagnosis** of myasthenia gravis → improvement of symptoms (**Edrophonium IV + Atropine**).



Treatment of Myasthenia Gravis



1- Anticholine esterase:

❖ **Neostigmine** : is a reversible cholinesterase inhibitor □ inhibits the degradation of Acetylcholine(Ach) □ Accumulation of Ach.

↑ Acetylcholine concentration □ stimulate both Nicotinic (Nm in N-M junction) & Muscarinic receptors.

↑ **skeletal muscle power, used orally in treatment of myasthenia gravis.**



Neostigmine Substitutes



- ❖ **Pyridostigmine**
- ❖ **Ambenonium**

Reversible cholinesterase inhibitor

Preferred to neostigmine in myasthenia gravis :

- More specific.
- Longer duration of action.
- Fewer visceral side effects.
- ↑ selectivity on skeletal muscles compared to it.



Neostigmine Substitutes



Edrophonium		Pyridostigmine & Ambenonium
Selectivity:	Skeletal muscle	Skeletal muscle
Duration: 5 min	Short	Longer duration
Uses: 1- Diagnosis of M.gravis 2- ttt of myasthenic crisis due to under ttt (improve patient) 3- Diagnosis of cholinergic crisis due to over ttt		ttt of myasthenia gravis (more specific - longer duration)



Treatment of Myasthenia Gravis



2- Atropine:

Atropine causes reversible competitive blockade of the actions of Ach at muscarinic receptors (**non-selective muscarinic receptors blocker**).

Atropine is added to block the unwanted side effects of reversible anticholine esterase which result from stimulation of muscarinic receptors by the accumulated Acetylcholine.



These unwanted side effects are:

- **Muscarinic:**

Bradycardia, hypotension, bronchospasm, miosis, vomiting, diarrhea, increase secretions (sweating, salivation, bronchial and lacrimation).

- **Nicotinic:**

Sk. Muscle twitches, eye lid, facial, trunk.



Treatment of Myasthenia Gravis

3- Adjuvant ttt:

a- Ephedrine: Potentiates Neostigmine
(VD of skeletal BV + facilitate NM transmission)

b- Caffeine: Potentiates Neostigmine
(Direct stimulation of ms)



4- Others:

a- Immunosuppressants as corticosteroides : Decrease antibody formation.

b- Plasmapheresis to wash acetylcholine receptor antibodies from the circulation.

c- Thymectomy.



Immunomodulating therapy



Corticosteroids

- Corticosteroids can suppress the immune system in several ways.
 - Prednisone has been shown to reduce acetylcholine receptor antibody levels

Azathioprine

- Azathioprine (Imuran) is an antimetabolite that blocks T lymphocytes proliferation.
- Azathioprine is used most often in patients who have relapsed while on prednisone or as a steroid-sparing agent in patients who have been taking prednisone for long periods of time



Immunomodulating therapy



Cyclosporine

- Cyclosporine (Sandimmune, Neoral), a drug designed to prevent rejection in organ transplantation patients
- Inhibits T cell proliferation by inhibiting IL-2 secretion.

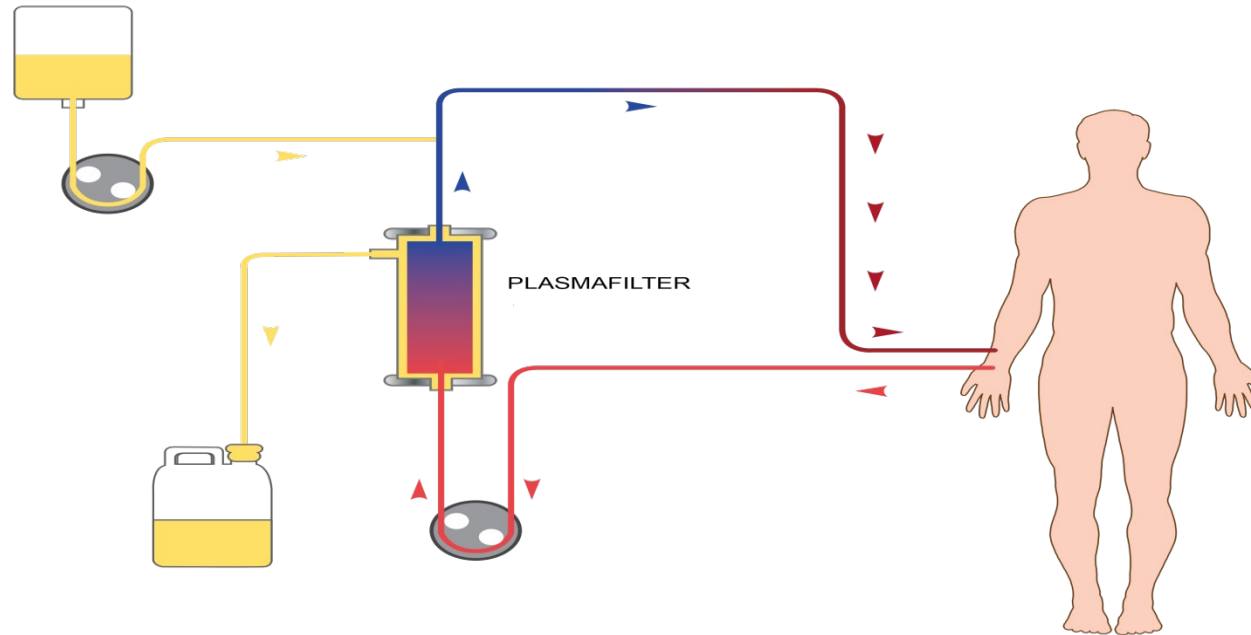
Mycophenolate Mofetil

- MyM (CellCept) is another immunosuppressive agent used in organ transplantation.
- By selectively blocking purine synthesis it suppresses both T- and B-cell proliferation.

Intravenous Immunoglobulin



Plasmapheresis



- Plasmapheresis, a procedure that removes acetylcholine receptor antibodies from the circulation.
- **Improvement following plasmapheresis occurs within a few days, much faster than for other immunomodulating therapies.**
- Plasmapheresis is an established therapy for patients in myasthenic crisis



Drugs contraindicated in Myasthenia Gravis



- 1-Skeletal muscle relaxants
- 2-Aminoglycosides
- 3-Lithium
- 4-Beta blockers e.g. propranolol
- 5-Anti-arrhythmics e.g. quinidine & lidocaine



Summary of Myasthenia Gravis



Autoimmune disease characterized by muscle weakness & easy muscle fatigability due to formation of antibodies against Motor End Plate (M.E.P.)

Diagnosis:

Edrophonium IV + Atropine

Treatment:

1- Antich. esterase: Neostigmine or pyridostigmine

2- Atropine: block unwanted muscarinic actions.

3- Adjuvant ttt: a- Ephedrine: b- Caffeine

4- Others: a- Cortisol b- Plasmapheresis c-

New Five Year Program
Thymectomy

Musculoskeletal & Integumentary Module



Lecture Quiz



1)- The following drug is contraindicated in myasthenic patients:

- a- Aminoglycoside
- b- Ephedrine
- c- Caffeine
- d- Cortisol

a- Aminoglycoside



Lecture Quiz



2)- The following drug is used in the diagnosis of myasthenic patients:

- a- Pyridostigmine
- b- Ambenonium
- c- Edrophonium
- d- Lithium

c- Edrophonium



Lecture Quiz



3)- All of the following drugs are used in the treatment of myasthenic patients EXCEPT:

- a- Pyridostigmine
- b- Neostigmine
- c- Atropine
- d- Curare

d- Curare



SUGGESTED TEXTBOOKS



1- Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2- Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.



THANK YOU

